

REMARKS

Claims 1-6, 8-16, 19, and 20 are pending in this application. Claims 1-6 and 8-16 are currently being examined and claims 19 and 20 remain withdrawn from consideration. By this Amendment, claim 7 is canceled and claim 1 is amended to incorporate the subject matter of canceled claim 7. No new matter is added.

I. **Status of Claims**

The Office Action requested clarification of the status of the claims. In the Amendment filed on February 15, 2005, Applicants inadvertently referred to claims 1-6, 8, 12-13 and 21-22. Claims 21-22 are not pending, and their reference was in error.

II. **Continuity Information**

Applicants confirm that this application is a Continuation in Part of U.S. Application No. 10/222,930 filed August 19, 2002. The specification was amended to include this continuity data by the December 15, 2003, Preliminary Amendment.

III. **Restriction / Election of Species Requirement**

Applicants affirm election of Group I, claims 1-6 and 8-16, with traverse. Furthermore, Applicants affirm election of species Cephalexin, with traverse. Applicants respectfully assert that at least claims 1, 6, 19 and 20 are generic to the elected species, that at least claims 1-6, 8-16, 19, and 20 read on the elected species.

Withdrawn process claims 19-20 depend from product claim 1 and include all of its limitations. MPEP §821.04 states that if Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined. Because process claims 19 and 20 include all of the limitations of product claim 1, claims 19 and 20 must be rejoined and examined with claim 1 upon allowance of claim 1. Furthermore, Applicants understand that upon search, examination, and allowance of the elected species,

search and examination will continue as to the non-elected species within the scope of the generic claims. In order to streamline prosecution and avoid delay, Applicants respectfully request withdrawal of the Restriction / Election of Species Requirement.

IV. Double Patenting Rejection

The Office Action provisionally-rejects claims 1-16 under the judicially-created doctrine of obviousness-type double patenting over claims 1-3, 5, and 6 of U.S. Patent Application No. 09/928,466 (which issued as U.S. Patent No. 6,932,981 to Sen et al. on August 23, 2005).

Claim 7 is canceled, rendering the rejection of this claim moot.

Applicants respectfully assert that the double-patenting rejection is improper, as U.S. Patent No. 6,932,981 is not commonly-owned with the instant application. The instant application is owned by ORCHID CHEMICALS & PHARMACEUTICALS LIMITED, based on the Assignment filed on August 18, 2003, and recorded at Reel 014233, Frame 0345. On the other hand, U.S. Patent No. 6,932,981 is assigned on its face to LUPIN LABORATORIES, LTD. Furthermore, the Patent Office's PAIR database indicates that U.S. Patent No. 6,932,981 is owned by LUPIN LABORATORIES, LTD, based on the Assignment recorded at Reel 012476, Frame 0926.

Nevertheless, in the interest of advancing prosecution, Applicants respectfully submit that the claimed invention is patentable over Sen.

Independent claim 1 recites a sustained release pharmaceutical composition comprising a cephalosporin antibiotic, a mixture of polymers comprising of galactomannans and neutral swellable polymers, and other pharmaceutically acceptable excipients, wherein the galactomannans used are selected from the group consisting of xanthan gum, guar gum and locust bean gum. Such a sustained release pharmaceutical composition is not taught or suggested by Sen.

Sen is directed to a fast disintegrating controlled release oral composition comprising a core material containing cefuroxime axetil present as controlled release form, the cefuroxime axetil being provided with an outer coating of a copolymer selected from aqueous dispersions of enteric methacrylic acid and methacrylic acid esters anionic copolymers having carboxyl group as the functional group or mixtures thereof (such as Eudragit L and S) and an inner coating of a sustained-release copolymer selected from aqueous dispersions of acrylate and methacrylate pH independent copolymers having quaternary ammonium group as a functional group or mixtures thereof, and optionally probenecid. Additionally, the coating composition may contain plasticizers. The composition is suitable for once daily administration. Sen at Abstract.

The combination of polymers disclosed in Sen is a combination of pH-dependent and pH-independent polymers. In Sen, the outer coating comprises pH-dependent polymers, such as an aqueous dispersions of methacrylic acid copolymers with carboxyl groups (Such as Eudragit L and S), which polymers become soluble above pH 5.5 and 7.0, respectively. The inner coating comprises pH-independent polymers, such as an aqueous dispersion of methacrylic acid copolymers having a quaternary ammonium functional group, the solubility of which is not dependent upon pH.

In contrast, the claimed invention requires a combination of pH independent polymers belonging to different chemical classes, which behave differently in gastric fluids. That is, claim 1 requires a mixture of polymers comprising of galactomannans and neutral swellable polymers, where the galactomannans are selected from xanthan gum, guar gum and locust bean gum. For example, xanthan gum is a naturally occurring anionic heteropolysaccharide gum derived from aerobic fermentation of *Xanthomonas campestris*. It contains D-glucose, D-mannose, D-glucuronate in the molar ratio of 2.8:2.0:20 and is partially acetylated with about 4.7 acetyl. It is a viscolyzing agent and helps to maintain the integrity of the dosage

form along with helping the sustained release of the drug from the matrix. The viscosity of aqueous solutions of xanthan gum is not significantly affected by changes in the pH of the solution between 1 and 11, and thus is pH-independent.

The other polymer used in the claimed sustained release pharmaceutical composition is a neutral swellable polymer. For example, an exemplary neutral swellable polymer is Eudragit NE 30 D poly(ethyl acrylate:methyl methacrylate) 2:1. This polymer is basically a methacrylic ester copolymer, and has no functional group as compared to the copolymers of Sen.

The claimed invention and Sen thus differ at least in that the polymers of the claimed invention are both pH-independent. Sen, however, requires the presence of at least one pH-dependent polymer.

Furthermore, the claimed invention and Sen differ at least in the classes of polymers used. The two types of polymers used in the claimed invention chemically belong to different chemical classes, one being a galactomannan selected from xanthan gum, guar gum and locust bean gum, and the other being a neutral swellable polymer. In contrast, Sen specifies that both polymers belong to the same group of methacrylic acid copolymers. Still further, the two polymers of the claimed invention also differ in their physical characteristics, namely that the galactomannan such as xanthan gum is soluble in water whereas the neutral swellable polymer such as Eudragit NE 30 D remains water insoluble throughout the entire pH range of the gastrointestinal tract.

Accordingly, the claimed invention is different from and is not disclosed in Sen. Further, it would not have been obvious to one of ordinary skill in the art to predict how a combination of pH-independent polymers (i.e., a galactomannan such as xanthan gum and a neutral swellable polymer such as Eudragit NE 30 D), which belong to different chemical classes and having different physical characteristics, would behave in the varying chemical

environment along the gastrointestinal tract and what would be their release mechanism in combination. It would not have been obvious to substitute the claimed polymers for the polymers disclosed as required in Sen, to practice the claimed invention. Sen does not teach or suggest such a combination of pH independent polymers.

A combination of the claimed polymers also provides unexpected results over use of one of the polymers alone. For example, it was found that when xanthan gum was used alone, the initial release of contained cephalosporin was rapid; when Eudragit NE 30 D was used alone, the integrity of the formulation was lost after 2 hours. However, it was surprisingly found that when a formulation comprising a combination of xanthan gum and Eudragit NE 30D comes into contact with the aqueous media of the GI tract, the thin film of eudragit controls the penetration and initial erosion of the xanthan gum and subsequently the release was uniform over a period of time due to hydration of xanthan gum to form a gel. In contrast, the polymers of Sen are provided to provide quick release.

In Sen, the composition is formulated such that it rapidly disintegrates into controlled release coated granules; wherein the entire outercoating comprising methacrylic acid copolymers with a carboxy group dissolves or erodes completely as pH increases. According to the claimed invention, however, the neutral swellable polymer such as NE 30D forms a sponge-like structure and slowly hydrates without disrupting the hydrophilic composition formed by the heteropolysaccharide (such as Xanthan gum). The sponge-like structure behaves as an inert matrix, and once the a galactomannan such as xanthan gum is completely hydrated, it forms a gel and then the release of the active ingredient is governed by diffusion through pores, channels and capillaries of the insoluble polymer composition. The integrity of the formulation is maintained over a substantial period of release.

Therefore it would not have been obvious to one skilled in the art how a sustained release matrix would perform and how the release profile would be when polymers of

different properties are used. Modification of Sen to practice the claimed invention would thus not have been obvious to one of ordinary skill in the art.

For at least these reasons, the claimed invention is patentable over Sen.

Reconsideration and withdrawal of the rejection are respectfully requested.

V. §103 Rejection

The Office Action rejects claims 1-16 under 35 U.S.C. §103(a) over Arora (U.S. Patent No. 5,948,440) and Zhang (U.S. Patent No. 6,083,532). Applicants respectfully traverse this rejection.

Claim 7 is canceled, rendering the rejection of this claim moot.

Claim 1 recites: "A sustained release pharmaceutical composition comprising a cephalosporin antibiotic, a mixture of polymers comprising of galactomannans and neutral swellable polymers, and other pharmaceutically acceptable excipients, wherein the galactomannans used is selected from the group consisting of xanthan gum, guar gum and locust bean gum."

The Office Action argues that it would have been obvious to one of ordinary skill in the art to prepare a sustained release formulation of cephalosporin antibiotic, a galactomannan and a mixture of polymers because the prior art allegedly teaches a pharmaceutical composition for controlled release of an active ingredient in which the composition comprises cefaclor, cephalexin, or their pharmaceutically acceptable hydrates, salts or esters, and a mixture of hydrophilic polymers of different viscosities. The Office Action further argues that the prior art teaches a tablet for sustained release of a drug comprising xanthum gums. Applicants respectfully disagree with the Office Action.

Arora discloses a modified release pharmaceutical composition in the form of a tablet of cephalexin or cefaclor and a mixture of hydrophilic polymer of different viscosity selected from the group consisting of at least one hydroxypropyl methylcellulose and at least one

hydroxypropylcellulose. See the Abstract of Arora. Zhang discloses a formulation of the pharmaceutical and a three-component release rate controlling matrix composition. See the Abstract of Zhang. The three components of the matrix composition are: 1) a pH dependent gelling polymer such as alginate component; 2) an enteric polymer component such as Eudragit L or S; and 3) a pH independent gelling polymer such as hydroxypropyl methylcellulose or polyethylene oxide. See the Abstract of Zhang.

The two types of polymers required in claim 1 are chemically very different from the polymers of the cited references and from each other. As a result, they also differ in their physical characteristics, chemical properties, and effects and properties in the gastric fluids. Generally, the galactomannans are soluble in water (see page 8, lines 29-35 of the specification), whereas the neutral swellable polymers remain water insoluble throughout the entire pH range in the gastrointestinal tract (see page 10, lines 5-9 of the specification). Neither Arora nor Zhang teach or suggest that such a combination of polymers that are soluble in different solvents should or could be used to provide a suitable sustained release pharmaceutical composition, as claimed.

Applicants submit that one of ordinary skill in the art would not have looked to the general teachings of Arora and/or Zhang to arrive at the specific composition recited in claim 1. Both Arora and Zhang teach a general release formulation comprising a variety of polymers. Neither Arora nor Zhang teach or suggest the specific combination recited in claim 1. Specifically, Arora and/or Zhang do not teach or suggest the specific sustained release pharmaceutical composition comprising a cephalosporin antibiotic, a mixture of galactomannans (selected from among xanthan gum, guar gum and locust bean gum) and neutral swellable polymers, as required in claim 1.

Arora and Zhang, in combination or alone, do not teach or suggest the sustained release pharmaceutical composition recited in claim 1. Specifically, neither Arora nor Zhang

teaches or suggests a sustained release pharmaceutical composition comprising a cephalosporin antibiotic and a mixture of galactomannans and neutral swellable polymers as required in claim 1. Claim 1 has been amended to further recite that the galactomannans are from among xanthan gum, guar gum or locust bean gum.

For at least the reasons discussed above, Arora and Zhang, alone or in combination, fail to teach or suggest all of the limitations recited in claim 1. Thus, claim 1 is patentable over Arora and Zhang, alone or in combination. Claims 2-6 and 8-18 depend from claim 1 and include all of its limitations. Accordingly, these dependent claims are patentable over Arora and Zhang, alone or in combination, for at least the same reasons as claim 1.

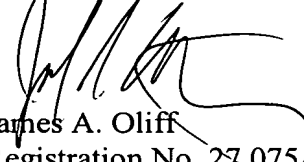
Reconsideration and withdrawal of the rejection are thus respectfully requested.

VI. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1-6, 8-16, 19, and 20 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



James A. Oliff
Registration No. 27,075

Joel S. Armstrong
Registration No. 36,430

JAO:JSA

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OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

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